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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,009	03/28/2005	Constantin G. Ioannides	UTSC:711US/10410987	7673

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,009	IOANNIDES ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8,10,12-32 and 44-55* is/are pending in the application.

4a) Of the above claim(s) *6,7,10,12,13,16-19,25,30,32,44,45,48-50 and 52-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5,14,15,23,20-24,27-29,31,46,51* is/are rejected.

7)☐ Claim(s) *8, 26, 47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/6/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 3/6/09 is acknowledged and has been entered.

The Declaration of Inventor Dr. Constantin G. Ioannides filed 3/6/09 in response to the request for information under 37 CFR 1.105 mailed 10/28/02 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election without traverse of Group I and species of SEQ ID NO: 11 (KIFGSLA-iso-Phe-L), as well as "an increase in the antigen's ability to protect CTL's from activation induced cell death" as the species of "modulation of immunity" in Applicant's amendment and responses filed 7/20/07 and 7/28/08. The Examiner notes that SEQ ID NO: 11 has the unnatural amino acid residue iso-Phe at position 8 (P8). Iso-Phe differs from Phe in that iso-Phe lacks the CH_2 group between the phenol ring and the peptide bond.

Claims 3, 8, 14, 15 and 28 read on the elected species.

Applicant is reminded that upon consideration of the prior art, examination had been extended to the species recited in instant claims 4, 5, 20-23, 26, 27, 29 and 31. Presently, upon consideration of the art, claims 24 and 51 are also being included in examination.

Claims 3-5, 8, 14, 15, 20-24, 26-29, 31 and newly added claims 46, 47 and 51 are presently being examined.

3. Applicant is reminded that the drawings are objected to because they contain handwritten text. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the Applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

4. Applicant's amendment filed 3/6/09 has overcome the prior rejection of record of claims 9 and 14 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

5. Applicant's amendment filed 3/6/09 has overcome the prior rejection of record of claims 1, 4, 5, 11, 14, 20-22, 28 and 29 under 35 U.S.C. 102(b) as being anticipated by Gillogly *et al* (FASEB J. 14: A147.18, 2000, Applicant's IDS reference "C19" in the Form 1449 filed 4/24/06) as evidenced by Castilleja *et al* (J. Immunol. 2002, 169: 3545-3554, IDS reference).

6. Applicant's amendment filed 3/6/09 has overcome the prior rejection of record of claims 1, 3, 4, 5, 8, 14, 15, 23 and 31 under 35 U.S.C. 102(b) as being anticipated by Baker *et al* (Immunity, 2000, 13: 475-484, IDS reference).

7. Applicant's amendment filed 3/6/09 has overcome the prior rejection of record of claims 1, 2, 4, 5, 8, 14, 20-23, 26 and 29 under 35 U.S.C. 102(a) as being anticipated by WO 01/36452 A2 (of record).

8. Applicant's amendment filed 3/6/09 has overcome the prior rejection of record of claims 1, 4, 5, 11, 14, 15, 20-22, 28 and 29 under 35 U.S.C. 103(a) as being unpatentable over in view of Gillogly *et al* (FASEB J. 14: A147.18, 2000, Applicant's IDS reference "C19" in the Form 1449 filed 4/24/06) in view of Fisk *et al* (J. Exp. Med. 1995, 181: 2109-2117, IDS reference) and Madden *et al* (Cell. 1993, 75: 693-708, IDS reference).

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 3-5, 14, 23, 27-29, 31 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Parker *et al* (J. Immunol. 1992, 149(6): 1896-1904, of record) as evidenced by an admission in the US 20050169934 A1 publication of the instant specification at [0036].

The instant rejection is necessitated by Applicant's amendment filed 3/6/09.

Parker *et al* teach making a T cell epitope analogue peptide, comprising changing P9 and P10 methionine of the antigenic peptide from influenza B nucleoprotein KLGEFYNQMM that binds to HLA-A2.1 to norleucine (*i.e.,* KLGEFFNQnornor). Parker *et al* teach that the analogue peptide forms a more stable complex with HLA-

A2.1 as measured by dissociation rate of β2m (especially paragraph spanning pages 1897-1898, Table 1 and methods).

The admission in the disclosure of the US 20050169934 A1 publication of the instant specification at [0036] is that low avidity CTL against tumor/pathogen uses MHC binding peptides that have a CH_2 side chain that is extended (peptide type 2 agonists).

Although the art reference does not explicitly teach that the peptide analog modulates immunity by increasing the antigen's ability to selectively activate low avidity CTLs, the art reference does teach substitution with norleucine that extends the side chain relative to the residue in the native peptide, and the admission in the disclosure at the cited location is that low avidity CTL against tumor/pathogen uses MHC binding peptides that have a CH_2 side chain that is extended. In addition, the activation of low avidity CTL may correlate with an increase in the analog peptide's ability to protect CTLs from activation induced cell death. The art reference also teaches that the peptide analog forms a more stable complex with HLA-A2 than the native peptide, a property that is expected to increase the peptide's ability to selectively activate cytokine production. The substitution of norleucine at position 8 of the peptide is a substitution at a TCR contact residue, and may increase the affinity of the peptide for a TCR. Therefore, the claimed process appears to be the same as the process of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the process of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim 14 is included in this rejection because Parker *et al* inherently teach that the CTL epitope of the antigen prior to substitution has been "identified." Although the 20050169934 A1 publication of the instant specification provides examples of how one of skill in the art would be able to identify epitopes, the term "identifying" is not defined. Thus, the art reference teachings meet the claim limitation recited in claim 14.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the Examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 162 USPQ 541, 550 - 51 (CCPA 1969).

11. Claims 3-5, 14, 15, 24, 27-29 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Krebs *et al* (J. Peptide Science, 1998, 4: 378-388) as evidenced by an admission in the US 20050169934 A1 publication of the instant specification at [0036].

The instant rejection is necessitated by Applicant's amendment filed 3/6/09.

Krebs *et al* teach a method for preparing a peptide antigen KR**Hpa**IDKAAK that binds more stably to an MHC class I molecule HLA-B*2705 than the native CTL peptide epitope, said method comprising substituting at least a first amino acid residue located in a bacterial CTL epitope KR**G**IDKAAK with homophenylalanine (Hpa), a non-naturally occurring amino acid residue that has a longer side chain as compared with the side chain of the at least first amino acid residue in the native epitope. Krebs *et al* teach that the position 3 amino acid residue is a secondary or auxiliary anchor residue position that fine tunes allele specificity for peptide selection, and that these secondary or auxiliary anchors allow one to design peptides that have a higher affinity than the naturally selected antigens [by changing the auxiliary anchor amino acid residue]. The method taught by Krebs *et al* further comprises modeling the native CTL epitope in the MHC class I binding groove. Krebs *et al* teach that modified peptides are designed to optimally bind the HLA molecule by filling a hydrophobic binding pocket, in this instance pocket D, with nonencoded amino acid residues. Krebs *et al* further teach that the combination of altered MHC anchor positions with variations of the TCR contact area should enable development of a nonpeptidic ligand for class I (see entire reference).

The admission in the disclosure of the US 20050169934 A1 publication of the instant specification at [0036] is that low avidity CTL against tumor/pathogen uses MHC binding peptides that have a CH_2 side chain that is extended (peptide type 2 agonists).

Although the art reference does not explicitly teach that the peptide analog modulates immunity by increasing the antigen's ability to selectively activate low avidity CTLs, the art reference does teach substitution with homophenylalanine (Hpa) that extends the side chain relative to the residue in the native peptide, and the admission in the disclosure at the cited location is that low avidity CTL against tumor/pathogen uses MHC binding peptides that have a CH_2 side chain that is extended. In addition, the activation of low avidity CTL may correlate with an increase in the analog peptide's ability to protect CTLs from activation induced cell death. The art reference also teaches that the peptide analog forms a more stable complex with HLA-B*2705 than the native peptide epitope, a property that is expected to increase the peptide's ability to selectively activate cytokine production. Therefore, the claimed process appears to be the same as the process of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the process of

the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim 14 is included in this rejection because Krebs *et al* inherently teach that the CTL epitope of the antigen prior to substitution has been "identified." Although the 20050169934 A1 publication of the instant specification provides examples of how one of skill in the art would be able to identify epitopes, the term "identifying" is not defined. Thus, the art reference teachings meet the claim limitation recited in claim 14.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the Examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 162 USPQ 541, 550 - 51 (CCPA 1969).

12. Claims 3-5, 14, 15, 24, 27-29, 31 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Rognan *et al* (PNAS USA 1995, 92: 753-757) as evidenced by an admission in the US 20050169934 A1 publication of the instant specification at [0036].

The instant rejection is necessitated by Applicant's amendment filed 3/6/09.

Rognan *et al* teach a method for preparing a peptide antigen KR**Hpa**IDKAAK that binds more stably to an MHC class I molecule HLA-B*2705 than the native CTL peptide epitope, said method comprising substituting at least a first amino acid residue located in a bacterial CTL epitope KR**G**IDKAAK with homophenylalanine (Hpa), a non-naturally occurring amino acid residue that has a longer side chain as compared with the side chain of the at least first amino acid residue in the native epitope. Krebs *et al* teach that the position 3 amino acid residue is a secondary anchor residue position in peptides that bind to HLA-B*2705, and that nonnatural side chains such as homophenylalanine fit much better within pocket D than the residue in the natural epitope peptide, as determined by modeling both peptides in the binding groove, and with a higher calculated affinity for the substituted peptide which is borne out experimentally in an *in vitro* binding assay. Rognan *et al* further teach substituting position 5-7 amino acid residues D, K, and A, respectively with Aba-Aba-Aba (each with the non-natural amino acid residue 4-aminobutyric acid, *i.e.,* gamma-aminobutyric acid). Rognan *et al* teach that such substitution does not alter the binding affinity of the substituted peptide relative to the natural peptide epitope for HLA-B*2705 (see entire reference).

Although the art reference does not explicitly teach that the peptide analog modulates immunity by increasing the antigen's ability to selectively activate low avidity CTLs, the art reference does teach substitution with homophenylalanine (Hpa) that extends the side chain relative to the residue in the native peptide, and the admission in the disclosure at the cited location is that low avidity CTL against

tumor/pathogen uses MHC binding peptides that have a CH_2 side chain that is extended. In addition, the activation of low avidity CTL may correlate with an increase in the analog peptide's ability to protect CTLs from activation induced cell death. The art reference also teaches that the P3 Hpa peptide analog forms a more stable complex with HLA-B*2705 than the native peptide epitope, a property that is expected to increase the peptide's ability to selectively activate cytokine production. The substitution in the peptide analog at positions 5-7 may increase the affinity of the peptide for a TCR. Therefore, the claimed process appears to be the same as the process of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the process of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim 14 is included in this rejection because Rognan *et al* inherently teach that the CTL epitope of the antigen prior to substitution has been "identified." Although the 20050169934 A1 publication of the instant specification provides examples of how one of skill in the art would be able to identify epitopes, the term "identifying" is not defined. Thus, the art reference teachings meet the claim limitation recited in claim 14.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the Examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 162 USPQ 541, 550 - 51 (CCPA 1969).

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 3-5, 14, 23, 20-22, 27-29, 31 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parker *et al* (J. Immunol. 1992, 149(6): 1896-1904, of record) in view of Anderson *et al* (Cancer. Immunol. Immunother. 1999, 48: 401-410) as evidenced by an admission in the US 20050169934 A1 publication of the instant specification at [0036].

The instant rejection is necessitated by Applicant's amendment filed 3/6/09.

Parker *et al* teach a method of making a T cell epitope analogue peptide, comprising changing P9 and P10 methionine of the antigenic peptide from influenza B nucleoprotein KLGEFYNQMM that binds to HLA-A2.1 to norleucine (*i.e.,* KLGEFFNQnornor). Parker *et al* teach that the analogue peptide forms a more stable complex with HLA-A2.1 as measured by dissociation rate of β2m (especially paragraph spanning pages 1897-1898, Table 1 and methods).

Parker *et al* does not teach wherein the antigen is a tumor antigen such as HER-2.

Anderson *et al* teach a HER2 peptide that binds to HLA-A2 that is recognized by CD8+ TIL from ovarian tumors. The C85 peptide ELVSEFSRM is able to increase expression in the relative density of surface HLA-A2.1 molecules on T2 cells (*i.e.,* on TAP peptide transporter deficient cell line, exogenously added peptides stabilize class I expression at the cell surface), however, only slightly as compared to the twofold and threefold increase caused by two other HER2 peptides E89 and E75, respectively, that have leucine and valine at P9. In contrast, C85 has methionine at position 9.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have changed the P9 anchor residue of the C85 peptide taught by Anderson *et al* to norleucine as is taught for the viral antigenic HLA-A2.1-binding peptide of Parker *et al* .

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to arrive at a better binding peptide for HLA-A2.1 that would stabilize HLA-A2.1 on the surface of T2 cells (*i.e.,* make a target cell that expresses high levels of the peptide/HLA complex), for the purpose of studying CTL in ovarian cancer patients.

The admission in the disclosure of the US 20050169934 A1 publication of the instant specification at [0036] is that low avidity CTL against tumor/pathogen uses MHC binding peptides that have a CH_2 side chain that is extended (peptide type 2 agonists).

Although the art reference does not explicitly teach that the peptide analog modulates immunity by increasing the antigen's ability to selectively activate low avidity CTLs, the primary art reference does teach substitution with norleucine that extends the side chain relative to the residue in the native peptide, and the admission in the disclosure at the cited location is that low avidity CTL against tumor/pathogen uses MHC binding peptides that have a CH_2 side chain that is extended. In addition, the activation of low avidity CTL may correlate with an increase in the analog peptide's ability to protect CTLs from activation induced cell death. The primary art reference also teaches that the peptide analog forms a more stable complex with HLA-A2 than the native peptide, a property that is expected to increase the peptide's ability to selectively activate cytokine production. Therefore, the claimed process appears to be similar to the process of the prior art absent a

showing of differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the process of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim 14 is included in this rejection because the CTL epitope of the antigen prior to substitution was "identified" by Anderson *et al*. Although the 20050169934 A1 publication of the instant specification provides examples of how one of skill in the art would be able to identify epitopes, the term "identifying" is not defined. Thus, the art reference teachings meet the claim limitation recited in claim 14.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the Examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 162 USPQ 541, 550 - 51 (CCPA 1969).

15. Claims 8, 26 and 47 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
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May 15, 2009

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644